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INITIAL SUBMISSION: LETTER R INTL ISOCYANATE INST INC TO USEPA RE V79 FIBROBLAST MICRONUCLEI INDUCTION BY CYSTEINE METHYL ESTER THIOL ACID ESTER CONJUGATE OF MDI, DATED 10/11/2000		
Chemical Category		
METHYLENE DIPHENYL DIISOCYANATE		

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INITIAL SUB-MISSION

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INTERNATIONAL ISOCYANATE INSTITUTE, INC.

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October 11, 2000

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Attn: 8(e) Coordinator

RE: Methylene diphenyl diisocyanate (MDI)
CAS 26447-40-5

Dear Sir/Madam:

The following information is being submitted by the International Isocyanate Institute (III) on behalf of its members[1] pursuant to current guidance issued by EPA indicating EPA's interpretation of Section 8 (e) of the Toxic Substance Control Act. Neither III nor any member of III has made a determination as to whether a significant risk of injury to health or the environment is actually presented by the findings. This information was provided to one our members as a courtesy. This was not a study sponsored by the Institute.

V79 FIBROBLAST MICRONUCLEI INDUCTION BY CYSTEINE METHYL ESTER THIOL ACID ESTER CONJUGATE OF METHYLENE DIPHENYL DIISOCYANATE (MDI). B Z Zhong, G Depree, D M[illegible]is and P D Siegel. NIOSH/HELD/ASB, Morgantown, WV, USA.

Isocyanates are known to react with thiols, rapidly and reversibly, underphysiological conditions. The biological significance of the possible formation of these thiol acid esters following exposure to diisocyanates used in polyurethane production, such as MDI, is not known. Reaction of MDI to cysteine or glutathione produced an insoluble product. A water soluble product was produced when MDI was reacted to cysteine methyl ester (CME). The resultant thiol acid ester (MDI-CME) was characterized by full NMR assignment and mass spectroscopy. Approximately 1.0 x 106 fibroblast in the exponential phase of growth were seeded into a 100 mm culture dish and cultured over night. The medium was changed to phosphate buffer saline (PBS) and the cells were exposed for 2 hrs to 1.25, 2.5, 5 or 10 µg/ml MDI-CME/PBS. Cells were washed and incubated for 20 hrs in culture medium with the cytokinesis blocker, Cytochalasin B. Cells were then washed, fixed, stained and scored for micronuclei (MN) in binucleated cells. Vehicle (water), CME, and positive vincristine sulfate controls were run, concurrently. MDI-CME caused a dose-dependent increase in MN. Significant increases in MN were noted at ≥2.5 µg/ml. A decrease in the nuclear division index denoting loss of

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[1] Members in the Americas Region: BASF Corporation, Bayer Corporation, Dow Chemical Company, Huntsman Polyurethanes and Lyondell.

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viability was noted at the highest dose (10 μg/ml). MDI-CME was more potent than the insoluble MDI thiol acid esters, as well as, the MDI hydrolysis product, 4,4'-methylenedianaline at inducing MN. Preliminary data also suggest that MN in alveolar macrophages may be increased in mice exposed to MDI-CME by intratracheal installation. These results underscore the need for investigation of the possible in vivo formation of MDI thiol acid esters following exposure to MDI.

Sincerely,

M.J. Blankenship
Managing Director

cc: J. Chapman
D. Gilbert
J. Jadlocki
J. Lyon
T. Landry
R. Robert
M. Spence

A 05

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